REMARKS

FORMAL MATTERS

Claims 132-139, 141, and 143-153 are pending after entry of the amendments set forth herein. Claims 132-139, 141, and 143-147 and 153 were examined and rejected. Claims 148-152 are withdrawn.

Claim 132 has been amended to require that the GPCR couples with Gi. Support for this amendment is found at, for example, page 4 line 4. No new matter is added.

Reconsideration of this application is respectfully requested.

REQUEST FOR REJOINDER

Per MPEP § 821.04, the Applicants respectfully requests that, upon allowance of Claim 132 with respect to the elected species, the Examiner rejoin all claims which depend from or otherwise require all the limitations of Claim 132.

A petition to rejoin claims 148 to 152 is filed herewith.

REJECTION OF CLAIMS UNDER 35 U.S.C. § 112, ¶1

Claims 132-134, 136-139, 141, 143-147 and 153 are rejected as not meeting the enablement requirement of 35 U.S.C. §112, first paragraph. This rejection is respectfully traversed.

Claim 132, from which all rejected claims depend, is directed to a screening method that employs a G protein-coupled receptor (GPCR) comprising an amino acid sequence having at least 90% identity to SEQ ID NO:3. SEQ ID NO:3 provides the amino acid sequence of a wild type human GPCR known as RUP41. Claim 153 recites a GPCR that "comprises an amino acid sequence having at least 95% identity to SEQ ID NO:3". The basis for this rejection relates in large part to the claims encompassing variants of the human and mouse RUP41 GPCRs that are explicitly disclosed in the specification. The question is one of skill in the art would make and use such molecules without undue experimentation.

The law relating to enablement is well established.

> When rejecting a claim under the enablement requirement of section 112, the PTO bears an initial burden of setting forth a reasonable explanation as to why it believes that the scope of protection provided by the claim is not adequately enabled by the description of the invention provided in the specification of the application.

In re Wright, 999 F.2d 1557, 1561-62 (Fed. Cir. 1993)

> "[T]he question of undue experimentation is a matter of degree. The fact that some experimentation is necessary does not preclude enablement; what is required is that the amount of experimentation 'must not be unduly extensive'".

PPG Indus., Inc. v. Guardian Indus. Corp., 75 F.3d 1558, 1564 (Fed. Cir. 1996)

> The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed to enable the determination of hot to practice a desired embodiment of the invention claimed.

PPG Indus., 75 F.3d 1564 (quoting *Ex parte Jackson* 217 USPQ 804 807 (BPAI 1982))

> Factors to be considered in determining whether a disclosure would require undue experimentation . . . include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

In re Wands, 858 F.2d 731, 737 (Fed. Cir. 1998).

In making this rejection, the Examiner argues that variants of SEQ ID NO:3 are not enabled because specification "fails to provide sufficient description information, such as definitive structural or functional features of the recited genus of GPCR variants and homologues. There is no description of the conserved regions that are critical to the structure and function of the genus recited. There is no description of the sites at which variability may be tolerated and there is no information regarding the relation of structure to function." Because the specification does not identify specific amino acids that are important for

RUP41 activity, the Examiner believes that it would be difficult or impossible to predict which RUP41 variants will retain activity.

However, predictability is but one of the factors in the Wand's analysis. The crux of the question whether, taking all the Wand's factors into account, practice of the claimed method would require undue experimentation.

The specification states that RUP41 is a GPCR that is coupled to Gi and inhibits adenylyl cyclase and cAMP production when stimulated. See page 3 line 33, page 4, line 4 and page 75 line 26 onwards. The specification describes the general structure/function relationship of GPCRs. See page 2, line 33 to page 3, line 19. The specification discloses the sequence of two allelic variants of human RUP41, as well as the sequence of mouse RUP41. See page 4, lines 35 to page 5, line 4. The specification provides guidance for making constitutively active mutants of RUP41. See page 56, lines 10-12. The specification describes a variety of methods for assaying GPCRs which can be used to test variant proteins for activity. See the section starting on page 40. The specification also describes a working example of a cell survival assay that employs RUP41. See section starting on page p. 76, line 24. This evidence is not disputed by the Examiner.

Moreover, the record shows that RUP41 is a member of an extremely well characterized family of proteins: the GPCRs. A search of NCBI's PubMed database reveals that there are well over 2900 journal articles, including 450 reviews, that have a publication date that precedes the priority date of the instant application (August 1, 2002) and contain the phrase "GPCR" OR "G protein-coupled receptor" in the abstract. See Exhibit A. Thus, at the priority date of the instant application, GPCR proteins were a subject of significant interest in the scientific community, and the level of skill in the art was very high. Moreover, the art in which the subject RUP41 protein belongs was therefore highly developed at the priority date of the instant application. For example, at the priority date of the instant application one of skill in the art would have knowledge of the atomic coordinates of at least one GPCR (see, e.g., reference A listed on Exhibit B). At the time of filing, the structure/function relationship of many GPCRs had been investigated (see, e.g., references B-H listed on Exhibit B), and several reviews on the structure/function relationship of GPCRs had been published (see, e.g., references I-O listed on Exhibit B). In addition, at the time of filing, one

of skill in the art would have been aware of several algorithms for predicting GPCR structure (see, e.g., references P and Q listed on Exhibit B), an algorithm for predicting important residues in GPCRs (see, e.g., reference R listed on Exhibit B), and reviews on the engineering of GPCRs by domain swapping (see, e.g., references S and T listed on Exhibit B). The Examiner has already been provided with these exhibits and references and does not dispute any of the statements made above.

The Applicant understands that the effect of amino acid substitutions cannot be predicted with absolute certainty. However, given the information in the instant specification and the deep general understanding of the structure and function of GPCR proteins, the Applicant submits that one of skill in the art would be make and use a large number of operable variants of RUP41 without undue experimentation.

The Applicants' conclusion is consistent with *Ex parte Kubin* (BPAI 2007; Appeal no. 2007-0819) which is a *precedential* decision by the BPAI. The grounds of the enablement rejection decided in *Ex parte Kubin* are similar to the grounds of rejection in the instant case in that in *Ex parte Kubin* a claim reciting "80% identity" language[1] was rejected as being non-enabled because there were no working examples other than SEQ ID NOS:1 and 2, and because very small changes in sequence, even one amino acid, can alter protein function. In this case, the Board acknowledged that although biotechnology is unpredictable, the other Wands factors, particular "the state of the art" and "the relative skill of those in the art" weigh more heavily in the Applicants' favor. In essence, the Board in *Ex parte Kubin* stated that "The amount of experimentation to practice the full scope of the claimed invention might have been extensive, but it would have been routine. The techniques necessary to do so were well known to those skilled in the art". Given the evidence described above and applying the logic of *Ex parte Kubin*, the Applicants submit that practice of the claimed method would not require undue experimentation, and this rejection should be withdrawn.

The Applicants also note that the BPAI has reversed several rejections based on similar grounds to those of this rejection. For example, in *Ex parte Liao* (BPAI 2008; Appeal

[1] Claim 73, the independent claim discussed in *Ex parte Kubin* recites: "An isolated nucleic acid molecule comprising a polynucleotide encoding a polypeptide at least 80% identical to amino acids 22-221 of SEQ ID NO:2, wherein the polypeptide binds CD48".

No. 2008-4364) the claims[2] were rejected because the specification did not identify any domain of EDG-1 that was critical for EDG-1 activity. Like RUP41, EDG-1 is a GPCR. In this case, the Board recognized that the effect of amino acid substitutions can be unpredictable. However, the rejection was reversed because although one of skill in the art might have been required to make and test every EDG1 variant encompassed by the claims, the claims were nevertheless enabled because the level of skill in the art is high (particularly because EDG-1 is a GPCR) and the experimentation would have been routine. Likewise, in *Ex parte Heck* (BPAI 2008; Appeal No. 2008-2875[3]), the Board noted that "some deletions and mutations will reduce activity". However, the Board reversed the rejection because "the amount of experimentation to practice the full scope of the claimed invention might be extensive, such experimentation would have been routine." Similarly, in *Ex parte Abad* (BPAI 2007; Appeal No. 2007-4356[4]), the Board again noted "any particular mutation in a protein sequence, even a conservative mutation, may result in an unpredictable change in the activity or function of a particular protein". In this case, the Board reversed the rejection because identifying active variants "would have required some experimentation in order to determine which nucleic acids would have pesticide activity and against which pests, but that experimentation would have been routine, not undue".

The Applicants understand that every case has its own set of facts that distinguishes that case from others. However, given the guidance in the instant specification, the vast amount of structural information on GPCRs available in the prior art, and the similarity of this case to the cases discussed in *Ex Parte Kubin*, *Ex parte Liao*, *Ex parte Heck* and *Ex parte Abad*, the Applicants believe that one of skill in the art would be able to practice the claimed method without undue experimentation. As such, this rejection should be withdrawn.

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[2] The claims appeal in this case were directed to a screening method that employed a polypeptide "having at least 95% identity to an amino acid sequence of SEQ ID NO:5".

[3] The claims appeal in this case were directed to an isolated polynucleotide that is "at least about 98% identity" to SEQ ID NO:1.

[4] The claims appeal in this case were directed to an isolated nucleotide acid "having at lest 90% sequence identity to" SEQ ID NO:3, wherein the sequence encodes a pesticidal polypeptide.

The Examiner is requested to reconsider this rejection in view of the foregoing discussion.

CLAIM OBJECTIONS

Claims 135 and 144 are objected to for allegedly reciting non-elected subject matter.

The Applicants kindly request rejoinder of the non-elected species upon allowance of claim 132.

Conclusion

A timely Notice of Allowance is requested.

If the Examiner finds that a telephone conference would expedite the prosecution of this application, please telephone the undersigned at the number provided.

The Commissioner is hereby authorized to charge any underpayment of fees associated with this communication, including any necessary fees for extensions of time, or credit any overpayment to Deposit Account No. 50-0815, order number AREN-027.

Respectfully submitted,
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